SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Device Generic Name:	An immunoassay for the qualitative detection of Antibody to Hepatitis B Surface Antigen (Anti-HBs Assay)
Device Trade Name:	ADVIA Centaur® Anti-HBs ReadyPack Reagents ADVIA Centaur® Anti-HBs ReadyPack Calibrators
Name and Address of Applicant:	Bayer Health Care LLC Diagnostic Division 511 Benedict Avenue Tarrytown, NY 10591-5097

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P030029

Date of Notice of Approval to Applicant: May 14, 2004

II. INDICATIONS FOR USE

ADVIA Centaur® Anti-HBs ReadyPack Reagents

The ADVIA Centaur® Anti-HBs assay is an *in vitro* diagnostic immunoassay for the qualitative determination of total antibodies to hepatitis B surface antigen in human serum or plasma (EDTA or heparinized) using the ADVIA Centaur System. The assay results may be used as an aid in the determination of susceptibility to hepatitis B virus (HBV) infection in individuals prior to or following HBV vaccination or where vaccination status is unknown. Assay results may be used with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection. A reactive assay result will allow a differential diagnosis in individuals displaying signs and symptoms of hepatitis in whom etiology is unknown.

QC Anti-HBs (aHBs)

For *in vitro* diagnostic use in monitoring the performance of the Anti-HBs assay on the ADVIA Centaur® Systems. The performance of the Anti-HBs quality control material has not been established with any other Anti-HBs assays.

III. CONTRAINDICATIONS – None Known.

IV. WARNINGS AND PRECAUTIONS

Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients, cord blood, neonatal specimens, infants, or children.
This assay has not been FDA cleared or approved for the screening of blood or plasma donors.
United States federal law restricts this device ot sale by or on the order of a physician. For in vitro diagnostic use only.
Assay performance characteristics have not been established when the ADVIA Centaur Anti-HBs assay is used in conjunctiin with other manufacturers' assays for specific HBV serological markers. Users are responsible for establishing their own performance characteristis.

V. DEVICE DESCRIPTION

The ADVIA Centaur® Anti-HBs assay is a sandwich immunoassay using direct, chemiluminometric technology. Hepatitis B surface antigen (HBsAg; ad and ay) are covalently coupled to magnetic latex particles (MLP) in the Solid Phase. In the Lite Reagent, the HBsAg (ad and ay) is labeled with acridinium ester. Nonmagnetic latex particles are added from the ancillary well. The sample is incubated simultaneously with Lite Reagent, Solid Phase, and Ancillary Reagent. Antibody-antigen complexes will form if anti-HBs is present in the sample.

The system automatically performs the following steps:

- dispenses 100 µL of sample into a cuvette
- dispenses 50 µL of Ancillary Reagent and incubates for 2.75 minutes at 37°C
- dispenses 100 µL of Solid Phase and 50 µL of Lite Reagent, and incubates the mixture for 6.75 minutes at 37°C
- separates the Solid Phase from the mixture and aspirates the unbound reagent
- washes the cuvette with Wash 1
- dispenses 300 µL each of Acid Reagent and Base Reagent to initiate the chemiluminescent reaction

- reads the results in Relative Light Units (RLU) and converts the RLU to Index values from a stored master curve traceable to the World Health Organization (WHO) anti-Hepatitis B Immunoglobulin 1st - Reference Preparation (1977).

A direct relationship exists between the amount of anti-HBs activity present in the patient sample and the amount of RLUs detected by the system.

Calibration:

The ADVIA Centaur® Anti-HBs assay utilizes a factory set Master Curve. The Master Curve values are contained on the Master Curve card provided with each kit. The master curve and calibration are lot specific. The barcode reader or keyboard is used to enter the Master Curve values into the system. The 2 calibrators in the kit are run when the lot is first used or after expiration of the calibrator interval (28 days). If the calibration run is valid as determined by prearranged parameters, the values are stored and used to "normalize" test values to the Master Curve. The assay utilizes a cutoff of 1.00 Index value, which is equivalent to 10 mIU/mL in the anti-Hepatitis B Immunoglobulin 1st Reference Preparation. Individuals whose samples read at or above this level are considered to be immune from infection with HBV.

VI. ALTERNATE PRACTICES AND PROCEDURES

Determination of the presence of anti-HBs in patients may be achieved by using a number of commercially available, FDA licensed/approved, serological tests. When the results of such tests are evaluated in conjunction with a physician's assessment and biochemical test results, susceptibility to HBV can be excluded.

VII. MARKETING HISTORY

The ADVIA Centaur® Anti-HBs Assay is currently being marketed internationally in accordance with Section 802 of the FD & C Act in the following countries: Britian, Israel, Sweden, Australia, Austria, Italy, India, Greater China (Hong Kong), Singapore, Canada, South Korea, Africa, Poland, Germany, France, and the Netherlands.

This product has not been withdrawn from any of these markets for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Failure of the product to perform as intended, or errors in the use of the product, may lead to a false result. A false nonreactive result cannot be considered a public health risk, as the individual would either unnecessarily be vaccinated, or would be considered to have not recovered from an acute HBV infection.

A false reactive result could be considered a public health risk due to the fact that an individual would be considered to have been previously vaccinated, or had been previously exposed, and would be therefore immune to HBV. The risk is that an individual would not be vaccinated and would be at a higher risk of infection if exposed to HBV.

IX. SUMMARY OF NON-CLINICAL STUDIES

The applicant performed in-house studies in order to evaluate the following performance characteristics of the ADVIA Centaur® Anti-HBs assay: analytical sensitivity, cutoff determination and verification, potential cross-reactivity, interference, stability, microbiological contamination, matrix effects, sample handling and collection, sample carryover, and precision.

Analytical Sensitivity

The ADVIA Centaur® Anti-HBs assay standardization is traceable to anti-Hepatitis B Immunoglobulin 1st International Reference Preparation (IRP, 1977) with the assay cut off value of 1.00 Index assigned at 10 mIU/mL. A study was performed to verify the standardization to the IRP across the dynamic range of the assay, using dilutions of the IRP. The study data demonstrates good agreement between the ADVIA Centaur® Anti-HBs calibration and the WHO anti-Hepatitis B Immunoglobulin IRP (lot 17-2-77).

In a second study, the analytical sensitivity of ADVIA Centaur® Anti-HBs assay was evaluated at the assay cut-off value. The assay cut-off value is set to 10 mIU/mL, which is the internationally accepted threshold of protective immunity. The activity at the cut-off value was defined by using 3 kit lots to assay a series of dilutions of the IRP near the cut-off value. The activity at the cut-off value in the ADVIA Centaur® Anti-HBs assay was 10.53 mIU/mL (95% confidence interval = 10.03 to 11.03 mIU/mL) as estimated by linear regression.

Cross-Reactivity

The ADVIA Centaur® Anti-HBs assay was evaluated for potential cross-reactivity to other disease states, viruses, microorganisms or historically problematic specimens. Three hundred thirty-three distinct serum and plasma specimens from 15 groups of potential cross-reactants were tested. The nonreactive anti-HBs status of each specimen was verified using a commercially available FDA approved anti-HBs assay. The following results were obtained on the ADVIA Centaur Anti-HBs assay:

		ADVIA Centaur Anti-HBs Results	
Clinical Category	***Number Tested***	***Nonreactive***	***Reactive***
Hepatitis A Infection (HAV)	15	15	0
Hepatitis C Infection (HCV)	11	11	0
Cytomegalovirus (CMV)	49	49	0
Epstein-Barr Virus (EBV)	15	15	0
Herpes Simplex Virus (HSV)	10	10	0
Varicella Zoster Virus (VZV)	18	18	0
Parvovirus B19 Infection	3	3	0
Rubella	85	85	0
Human Immunodeficiency Virus (HIV-1 & HIV-2)	41	40	1
Toxoplasmosis	9	9	0
Syphilis	15	14	1
Non Viral Liver Disease	10	10	0
Rheumatoid Arthritis	12	12	0
Autoimmune Disease (Systemic Lupus & ANA)	7	7	0
Influenza Vaccine Recipients	33	33	0
Total Samples Tested	333	331	2

Interfering Substances

A study was performed to evaluate the ADVIA Centaur® Anti-HBs assay for interference to high levels of endogenous substances, specifically, conjugated bilirubin @ 20 mg/dL, unconjugated bilirubin @ 40 mg/dL, hemoglobin @ 500 mg/dL, triglycerides @ 1000 mg/dL, and human serum albumin @ 12 g/dL (ie, high total protein). The study was designed using the protocol described in guidance document NCCLS EP7-P[1]. The interference testing was performed using specimens from 5 individuals and evaluated in 4 specimen matrices: serum, serum gel-barrier tubes, EDTA plasma , and lithium heparin. The anti-HBs activity of the specimens spanned a range of approximately 8 mIU/mL to 48 mIU/mL. There was 1 negative specimen. Average dose recoveries of the spiked test specimens were within 15% of the average matched control specimens. No clinically significant changes were observed.

A study was performed to evaluate the ADVIA Centaur® Anti-HBs assay for interference in specimens with high levels of immunoglobulin (6 g/dL) or low total protein (3 g /dL). The study was designed via the protocol described in guidance document NCCLS EP7-P[1]. The interference testing was performed using 9 serum and EDTA specimens (8 anti-HBs positives, 1 anti-HBs negative). The anti-HBs activity in these samples spanned a range from approximately

[1] National Committee for Clinical Laboratory Standards; Interference Testing in Clinical Chemistry; Proposed Guidelines (1986); NCCLS document EP7-P.

13 mIU/mL to >1000 mIU/mL. Average dose recoveries of the spiked test specimens were within 15% of the average matched control specimens. No clinically significant changes were observed.

Interference Table.

Serum specimens that are . . .	*Demonstrate <15% change in results up to . . .*
hemolyzed	500 mg/dL of hemoglobin
lipemic	1000 mg/dL of triglycerides
icteric	20 mg/dL of conjugated bilirubin
icteric	40 mg/dL of unconjugated bilirubin
proteinemic (high)	12 g/dL of total protein
proteinemic (low)	3 g/dL of total protein
hyper IgG	6 g/dL of immunoglobulin G

Interference testing was determined according to NCCLS Document EP7-P.[1]

Stability Studies

Five lots of anti-HBs reagents and 4 lots of calibrators and controls were placed on real-time stability studies. All kits and reagents were stored at the recommended storage temperature of 2°C to 8°C. Reagents and calibrators were monitored at several checkpoints after the manufacturing date. Shipping studies of the reagents found that the anti-HBs reagents could withstand 3 freeze/thaw cycles (-40°C to 4°C) without aggregation of the solid phase and with acceptable performance. Studies also tested for shipment of upside-down packs. ReadyPack reagents stored upside down could tolerate up to 52 weeks in this position, although the recommended shipping condition is upright at 2°C to 8°C. The anti-HBs calibrators and controls also underwent 3 freeze/thaw cycles with no adverse effects.

The studies support a claim of 52-week expiration dating for the anti-HBs ReadyPack reagents, calibrators, and controls. The recommended shipping and storage conditions are to ship the ReadyPack reagents upright at 2°C to 8°C and store at 2°C to 8°C.

Reagent On-Board Stability Studies

Three lots of reagent were tested as part of reagent on-board stability (OBS) studies on 5 ADVIA Centaur® instruments. On-Board Stability testing on the instruments occurred at several checkpoints after the pack seal was pierced. A fresh (unpierced pack) served as the control for each time point. The dose recovery within 10% of the fresh pack defined acceptable performance. Similarly, evaluation of the dose recovery results from the pierced pack compared to the fresh pack at the first calibration point set the re-calibration interval on the ADVIA Centaur® instrument.

The OBS studies for the reagents support 41 days OBS for the ADVIA Centaur® Anti-HBs reagents. The OBS studies also support a re-calibration interval of 28 days.

Stress Studies of Calibrators and Controls

A calibrator and control OBS study was performed to evaluate the length of time a calibrator or control sample could remain in an open sample tube at an elevated temperature (30°C). The acceptance criteria were RLU recovery within 15% of the time-zero result. The high calibrator and positive controls were most sensitive to elevated temperature. The data supports 8 hours OBS for the anti-HBs calibrators and controls.

The calibrator and control open bottle use study examined the length of time the calibrators or controls were stable once the vial was opened. Open vials were stored at the recommended storage conditions of 2°C to 8°C. The open bottles were sampled periodically up to 95 days after the initial opening. Fresh (unopened) bottles were evaluated at each time point and served as controls. The acceptance criteria for this study were dose recovery within 10% (or 2SD) of the fresh bottle dose. The study supports an open bottle use lifetime of up to 90 days.

Microbiology Studies

The ADVIA Centaur® Anti-HBs reagents and controls contain a preservative to protect against adventitious contamination by microorganisms. Reagents and controls were challenged in a study conducted according to USP 23/NF 18. The preservative study results indicated complete and effective elimination of all of the microorganisms. The study was repeated with the reagents and controls after 24 months of storage with the same level of preservative efficacy. The reagents were tested against the product release panel after challenge with the microorganisms and passed all specifications.

Matrix Studies

The ADVIA Centaur Anti-HBs assay can use plasma specimens collected using either heparin or EDTA anticoagulants. In a matched matrix study of 25 specimens around the cutoff (Index Value 1.0), drawn in three tube types including serum, EDTA and Li-heparin vacutainer tubes, the recovery of the heparinized samples was 84% and the recovery of the EDTA samples was 94% of the serum control. N = 25 samples: (12 > 1.0 Index, 13 <1.0 Index)

Index Range: approximately 0.4 to 2.0 Index

Matrix Bias Study of Samples Near the Cutoff

Statistic	*Serum (Index)*	*EDTA (Index)*	*Li Heparin (Index)*
Mean	1.05	1.00	0.89
SD	0.53	0.56	0.56
Bias to Serum (Index)	NA	-0.06	0.16
SD of Bias	NA	0.05	0.05
Bias to Serum (% recovery)	NA	-5.3 %	-15.0%

The data demonstrated that Na and Li heparinized samples may cause lower Index Values in some anti-HBs reactive samples. High negative results (0.50–0.74 Index Value) obtained in samples collected with these anticoagulants should therefore be interpreted accordingly. It is recommended that additional testing be performed in either a serum or EDTA plasma. This information is provided in the Caution section of the labeling.

Precision Studies

The ADVIA Centaur Anti-HBs precision and reproducibility in various sample matrices was examined in a 20-day precision protocol (NCCLS EP5-A) using a single lot of reagents. Twenty spiked specimens in four matrices were prepared to measure the precision of the assay at different dose levels. In addition to serum matrix, the anticoagulants tested were K_2-EDTA, Na heparin, and Li heparin. The specimens were assayed in duplicate twice per day for 20 time points. A single instrument was used in this study over the course of 35 days. The matrix reproducibility results are presented in the following table. The precision estimates were derived from variance component analysis. Calculations for within run, between day, and total precision were performed as recommended by the guidance protocol.

Precision Estimates for Matrix Study

Member	Matrix	Mean Index Value[2]	Within Run[3] SD	Within Run[3] CV (%)	Between Days[4] SD	Between Days[4] CV (%)	Total[5] SD	Total[5] CV (%)	Number of Observations
S-7	Serum	0.77	0.123	16.3	0.05	6.8	0.14	17.7	80
S-12		1.19	0.09	7.5	0.00	0.0	0.12	10.0	80
S-15		1.49	0.08	5.4	0.00	0.0	0.12	8.3	80
S-100		9.24	0.27	2.9	0.00	0.0	0.46	5.0	80
S-200		19.87	0.64	3.2	0.21	1.1	0.87	4.4	80
E-7	EDTA	0.66	0.10	15.3	0.06	9.0	0.12	18.3	80
E-12	plasma	1.14	0.11	9.7	0.04	3.5	0.12	10.4	80
E-15		1.53	0.07	4.5	0.05	3.4	0.11	7.4	82*
E-100		9.68	0.26	2.7	0.00	0.0	0.58	5.9	80
E-200		19.41	0.51	2.6	0.23	1.2	0.73	3.7	80
Na-7	Na heparin	0.75	0.07	9.3	0.05	6.1	0.12	15.5	80
Na-12	plasma	1.13	0.07	6.5	0.03	2.3	0.09	8.2	80
Na-15		1.51	0.11	7.1	0.05	3.5	0.12	8.0	82*
Na-100		9.31	0.31	3.3	0.24	2.6	0.44	4.7	80
Na-200		19.54	0.63	3.2	0.15	0.8	1.37	7.0	80
Li-7	Li heparin	7.14	0.11	14.7	0.05	5.7	0.11	15.8	82*
Li-12	plasma	1.19	0.07	5.8	0.02	1.6	0.09	7.7	80
Li-15		1.40	0.14	9.6	0.00	0.0	0.17	12.0	80
Li-100		10.06	0.32	3.2	0.18	1.8	0.60	6.0	80
Li-200		19.92	0.67	3.3	0.43	2.2	0.97	4.8	80

! It is recommended that laboratories establish their own precision and reproducibility

ranges for plasma specimens.

2 Arithmetic mean of all results

3 Variability of the assay performance within run

4 Variability of the assay performance between days

5 Variability of the assay performance incorporating all days and runs.

* - Differences in the number of observations were due to routine laboratory practices.

Reproducibility

The ADVIA Centaur Anti-HBs reproducibility study was performed at 3 external sites using 2 reagent lots per site. A 5-member panel and controls were assayed in replicates of 5 on a single run per day over 6 days for each lot. The study was completed with a single calibration of the assay. The data from all 3 sites and from all 3 reagent lots were combined to obtain SD and percent CV for within run, between run, between testing site, between lot, and total. The precision estimates were derived from variance component analysis. The reproducibility results are presented in the following table:

Reproducibility Estimates for All Testing Sites and Reagent Lots

	Mean Index Value[1]	*Within Run*[2]		*Between Run*[3]		*Between Testing Site*[4]		*Between Lot*[5]		*Total*[6]		
Panel Member		*SD*	*CV (%)*	*SD*	*CV (%)*	*SD*	*CV (%)*	*SD*	*CV (%)*	*SD*	*CV (%)*	*Number of Observations*
1	0.02	0.023	NA	0.03	NA	0.012	NA	0.001	NA	0.04	NA	180
2	0.72	0.08	11.5	0.04	5.3	0.10	14.2	0.034	5.0	0.14	19.6	180
3	1.24	0.08	6.2	0.034	3.2	0.13	10.8	0.04	3.3	0.16	13.3	179*
4	1.50	0.089	5.8	0.05	3.0	0.123	8.5	0.04	2.9	0.17	11.1	178*
5	19.41	0.61	3.1	0.18	0.9	1.11	5.7	0.701	3.6	1.46	7.5	180
Negative Control	0.06	0.04	NA	0.05	NA	0.05	NA	0.00	NA	0.08	NA	179*
Positive Control	12.69	0.38	3.0	0.26	2.1	0.65	5.1	0.00	0.0	0.79	6.3	180

1 Arithmetic mean of all results (all testing sites and reagent lots)

2 Variability of the assay performance within day (all testing sites and reagent lots)

3 Variability of the assay performance between days (all testing sites and reagent lots)

4 Variability of the assay performance between testing sites (from testing site to testing site)

5 Variability of the assay performance between reagent lots (from reagent lot to reagent lot, across all testing sites)

6 Variability of the assay performance incorporating all testing sites, all reagent lots, and all days

* - Differences in the number of observations were due to routine laboratory practices.

NOTE: 5 replicates per panel in 1 run per day for 6 days

NA = not applicable.

X. SUMMARY OF CLINICAL STUDIES

Study Design:

A multi-center prospective study for the ADVIA Centaur® Anti-HBs assay consisted of 2197 patients. Of these 2197 patients, 966 patients (43.97%) were from the high risk population, 846 patients (38.51%) were from the signs and symptoms population, 212 patients (9.65%) were from the dialysis population, and 173 patients (7.87%) were from the vaccinee population. The prospective study population was 42.47% Caucasian, 22.58% Black, 25.81% Hispanic, 4.37% Asian, and 4.78% from unknown or other ethnicity. The majority of patients were male (52.48% male and 47.52% female). The mean age was 45.3 years (range of 12 to 82 years). Patients in the prospective study population were from the following geographic regions: Florida (36.96%), Texas (33.41%), New York (21.53%), California (7.74%), and Illinois (0.36%).

The ADVIA Centaur® Anti-HB expected value results for the prospective population for all sites combined by age group and gender are summarized in the following table.

Distribution of High Risk, Signs and Symptoms, Dialysis, and Vaccinee Population by Age Group and Gender (All Testing Sites)

Age (Years)	*Gender*	*Reactive (N)*	*Nonreactive (N)*	*Total (N)*
0-9	Male	0	0	0
	Female	0	0	0
10-19	Male	3	4	7
	Female	9	7	16
20-29	Male	56	51	107
	Female	83	45	128
30-39	Male	89	125	214
	Female	104	103	207
40-49	Male	154	239	393
	Female	164	161	325
50-59	Male	115	183	298
	Female	94	139	233
60-69	Male	34	54	88
	Female	49	57	106
≥ 70	Male	10	35	45
	Female	8	20	28
Unknown	Male	1	0	1
	Female	0	1	1
Total	Male	462	691	1153
	Female	511	533	1044
	All	973	1224	2197

The HBV disease classification for each patient in the high risk, signs and symptoms, and dialysis populations (total of 2024 patients) was determined by serological assessment using resultant hepatitis marker profiles obtained from results of commercially available, FDA-approved reference assays. The serological assessment included the following 6 HBV markers: hepatitis B virus surface antigen (HBsAg), hepatitis B virus e antigen (HBeAg), total antibody to hepatitis B virus core antigen (Anti-HBc Total), IgM antibody to hepatitis B virus core antigen (Anti-HBc IgM), total antibody to HBeAg (Anti-HBe), and total antibody to hepatitis B virus surface antigen (anti-HBs) (quantitative). Testing of these specimens occurred at hospital associated diagnostic laboratories located in Miami, FL (34%), Dallas, TX (33%), and New York City, NY (33%). The individual ADVIA Centaur® HBV assay result was compared to the reference HBV assay result and to the patient classification. No patients were excluded from the complete study set due to incomplete reference HBV serological results.

Each patient's HBV infection was classified based on the reactive (+)/ nonreactive (–) patterns of the 6 HBV reference serological markers. Disease classification for each patient was based only on the HBV serological marker results, and was not affected by additional laboratory or clinical information. There were 31 unique reference marker patterns observed using the ADVIA Centaur® Anti-HBs assay. These patterns are presented in the following table.

Bayer ADVIA Centaur® Anti-HBs Assay Classification by HBV Reference Markers (All Testing Sites)						
HBV Reference Markers						HBV Classification
HBsAg[a]	HBeAg	IgM Anti-HBc	Total Anti-HBc	Anti-HBe	Anti-HBs (>10 mIU/mL)	
+	+	+	+	+	-	Acute
+	+	+	+	-	-	Acute
+	-	+	+	+	-	Acute
+	+	-	+	+	-	Chronic
+	+	-	+	-	+	Chronic
+	+	-	+	-	-	Chronic
+	-	-	+	+	+	Chronic
+	-	-	+	+	-	Chronic
+	-	-	+	-	+	Chronic
+	-	-	+	-	-	Chronic
+	+	+	+	-	+	Chronic
-	-	+	+	+	+	Early Recovery
-	-	+	+	+	-	Early Recovery
-	-	+	+	-	-	Early Recovery
-	-	+	+	-	-	Early Recovery
-	-	-	+	+	-	Early Recovery
-	-	-	+	+	+	Recovery
-	-	-	-	+	+	Recovery
-	-	-	+	-	+	Recovered
-	-	-	+	-	-	Recovered
-	-	-	-	-	+	HBV Vaccine Response
-	-	-	-	-	-	Not Previously Infected
+	-	-	-	-	+	Uninterpretable
+	-	-	-	-	-	Uninterpretable
-	+	-	-	-	+	Uninterpretable
-	+	-	-	-	-	Uninterpretable
-	-	+	-	-	-	Uninterpretable
-	-	-	-	+	-	Uninterpretable
-	+	-	+	-	+	Uninterpretable
-	+	-	+	-	-	Uninterpretable
-	+	-	+	+	+	Uninterpretable

+ = Reactive

- = Nonreactive

a Reactive (+) = Reference HBsAg assay result was reactive and confirmed to be reactive by neutralization
Nonreactive (-) = Reference HBsAg assay result was nonreactive, or reactive, but non-confirmed by neutralization

Note: when the result was 'EQUIVOCAL', it was assumed to be nonreactive (-)

Following the assignment of specimen classification, the HBV results obtained using the ADVIA Centaur® method were compared with results obtained using the reference method for each result category (reactive and nonreactive). The HBV

results from the ADVIA Centaur Anti-HBs assay and the reference assay for all testing sites combined is presented in the following table.

Comparison of Results in High Risk, Signs and Symptoms, and Dialysis Populations by HBV Classification
ADVIA Centaur Anti-HBs Assay versus Reference Anti-HBs Assay (All Testing Sites)[1]

	Reference Anti-HBs Assay Negative		*Reference Anti-HBs Assay Positive*		
HBV Classification	*ADVIA Centaur Anti-HBs Assay*		*ADVIA Centaur Anti-HBs Assay*		
	Reactive (N)	*Nonreactive (N)*	*Reactive (N)*	*Nonreactive (N)*	*Total (N)*
Acute	0	11	0	0	11
Chronic	4	100	5	3	112
Early Recovery	20	95	8	0	123
Recovery	0	0	198	13	211
Recovered	18	136	156	14	324
HBV Vaccine Response	0	0	359	26	385
Not Previously Infected	58	779	0	0	837
Uninterpretable	1	14	5	1	21
Total	101	1135	731	57	2024

1 In this study, 84 of 2024 specimens fell within the retest zone. Thirty-seven (44%) of these specimens were determined to be reactive after retesting.

The percent agreement between the ADVIA Centaur® Anti-HBs assay and the reference anti-HBs assay for the high risk, signs and symptoms, and dialysis populations across all testing sites is summarized in the following table.

ADVIA Centaur Anti-HBs Assay versus Reference Anti-HBs Assay (All Testing Sites) by HBV Classification in High Risk, Signs and Symptoms, and Dialysis Populations

HBV Classification	*Positive Percent Agreement % (x/n)*	*95% Exact Confidence Interval*	*Negative Percent Agreement % (x/n)*	*95% Exact Confidence Interval*
Acute			100 (11/11)	71.5 to 100
Chronic	62.5 (5/8)	24.5 to 91.5	96.1 (100/104)	90.4 to 98.9
Early Recovery	100 (8/8)	63.1 to 100	82.6 (95/115)	74.4 to 89.0
Recovery	93.8 (198/211)	89.7 to 96.7		
Recovered	91.8 (156/170)	86.6 to 95.4	88.3 (136/154)	82.2 to 92.9
HBV Vaccine Response	93.3 (359/385)	90.3 to 95.5		
Not Previously Infected			93.1 (779/837)	91.1 to 94.7
Uninterpretable	83.3 (5/6)	35.9 to 99.6	93.3 (14/15)	68.1 to 99.8
Overall	92.8 (731/788)	90.7 to 94.5	91.8 (1135/1236)	90.2 to 93.3

HBV Vaccinee Population Study

A study was conducted using 173 serum samples from individuals who had received a full course of injections of either Engerix-B® HBV vaccine (GlaxoSmithKline), Recombivax HB® HBV vaccine (Merck & Company, Inc.), the Twin RX Hepatitis A and B vaccine (GlaxoSmithKline), or another type of hepatitis B vaccine. All samples were assayed with a reference Anti-HBc total assay and found to be negative. Testing of these specimens occurred at hospital associated diagnostic laboratories located in Miami, FL (20%), Dallas, TX (37%), and New York City, NY (43%). Samples were tested using both the ADVIA Centaur® Anti-HBs assay and the reference anti-HBs assay, and the results were compared.

Comparison in Results in Vaccinee Population
ADVIA Centaur® Anti-HBs Assay vs. Anti-HBs Reference Assay {All Testing Sites}

	Reference Anti-HBs Negative		Reference Anti-HBs Positive		Total
	ADVIA Centaur® Anti-HBs Assay		ADVIA Centaur® Anti-HBs Assay		
	Reactive[1]	Nonreactive	Reactive	Nonreactive	
	N	N	N	N	N
Vaccinee	9	30	132	2	173

1. In this study, 6 of 173 specimens fell within the retest zone. Four (67%) of these specimens were determined to be reactive after retesting.

The percent agreement between the ADVIA Centaur® Anti-HBs assay and the reference anti -HBs assay for the vaccinee population is summarized in the following table.

Percent Agreement and Confidence Intervals in Vaccinee Population
ADVIA Centaur® Anti-HBs Assay and Reference Anti-HBs Assay

Testing Site	Positive Percent Agreement % (x/n)[a]	95% Exact Confidence Interval	Negative Percent Agreement % (x/n)[b]	95% Exact Confidence Interval
All Testing Sites	98.5 (132/134)	94.7 to 99.8	76.9 (30/39)	60.7 to 88.9

HBV Vaccination Panel Study

A study was conducted using 40 well-characterized, commercially available serum samples from 20 individuals prior to vaccination and after vaccination. Testing was

performed at one testing site in Miami, Florida. Samples were tested using both the ADVIA Centaur® Anti-HBs assay and the reference anti-HBs assay, and the results were compared. The method comparison for the vaccination panel population across all testing sites is presented in the following table.

Comparison of ADVIA Centaur Anti-HBs and Reference Anti-HBs Results in Pre- and Post-Vaccinated Populations[1]

	Reference AntiHBs Results		
ADVIA Centaur AntiHBs Results	Nonreactive (N)	Reactive (N)	Total (N)
Pre-vaccination			
Nonreactive, N (%)	20 (100%)	0	20 (100%)
Reactive, N (%)	0	0	0
Percent agreement: 100% 95% confidence interval: 83.2 to 100			
Post-vaccination			
Nonreactive, N (%)	0	0	0
Reactive, N (%)	0	20 (100%)	20 (100%)
Percent agreement: 100% 95% confidence interval: 83.2 to 100			

1. For the vaccinee panel (samples from 20 patients), the percent agreement between ADVIA Centaur Anti-HBs results and reference results was determined for pre-vaccination and for post-vaccination.

Based on all of the clinical laboratory study information presented, the following ADVIA Centaur® Anti-HBs assay result interpretation was established:

ADVIA Centaur® Anti-HBs Assay Result		
	Status	**Interpretation**
<1.00	Negative	Patient is assumed to not have immunity to HBV infection.
≥0.75 and <1.25	Retest Zone	If results are within the retest zone after initial testing, samples are to be retested. After retesting, if 3 results are available and 2 results are ≥ 1.0, then the sample is considered to be reactive. If 3 results are available and 2 results are < 1.0, then the sample is considered to be nonreactive.
≥1.00	Positive	Anti-HBs is detected at >10 mIU/mL. Patient is considered to have immunity to HBV infection.

XI. CONCLUSIONS DRAWN FROM STUDIES

The data from the non-clinical studies demonstrated acceptable analytical sensitivity and specificity, reproducibility, and stability of the ADVIA Centaur® Anti-HBs assay when used according to the instructions for use as stated in the labeling, the warnings and precautions, the Specimen Collection and Preparation and Limitations section of the labeling.

RISK BENEFIT ANALYSIS:

The nonclinical and clinical studies contained in this application demonstrated that the device is safe and effective as indicated. It can therefore be concluded that the benefits of the ADVIA Centaur® Anti-HBs assay, when used according to the provided directions and in conjunction with other serological and clinical information outweigh any risk that may be associated with its use.

The clinical studies in this application indicate that the ADVIA Centaur® Anti-HBs assay is safe and effective when used according to the directions for use in the labeling. The sponsor has provided scientific data to support the utility of this assay in conjunction with other laboratory results and clinical information as an aid in the laboratory determination for individual's susceptibility to HBV infection, for individuals prior to or following HBV vaccination, or where vaccination status is unknown. A reactive assay result will allow a differential diagnosis in individuals displaying signs and symptoms of hepatitis in whom etiology is unknown.

XII. PANEL RECOMMENDATIONS

In accordance with the provisions of section 515(c)(2) of the act as amended in the Safe Medical Devices Act of 1990, this PMA was not referred to the Microbiology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

FDA issued an approval order on May 14, 2004.

The applicant's manufacturing facilities were inspected on October 27, and November 11, 2003 and found to be in substantial compliance with the Quality Systems Regulation (21 CFR 820).

XIII. APPROVAL SPECIFICATIONS

Directions for Use: Refer to the labeling

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Cautions, Precautions and Limitations statements in the labeling.

Postapproval Requirements and Restrictions: See approval order.